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Antibiotics for ureaplasma in the vagina in pregnancy (Review)

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Raynes-Greenow CH, Roberts CL, Bell JC, Peat B, Gilbert GL, Parker S.
Antibiotics for ureaplasma in the vagina in pregnancy.
Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD003767.
DOI: 10.1002/14651858.CD003767.pub3.

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[Intervention Review]

Antibiotics for ureaplasma in the vagina in pregnancy

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Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 9, 2011.

Citation: Raynes-Greenow CH, Roberts CL, Bell JC, Peat B, Gilbert GL, Parker S. Antibiotics for ureaplasma in the vagina in pregnancy. *Cochrane Database of Systematic Reviews* 2011, Issue 9. Art. No.: CD003767. DOI: 10.1002/14651858.CD003767.pub3.

ABSTRACT

Background

Preterm birth is a significant perinatal problem contributing to perinatal morbidity and mortality. Heavy vaginal ureaplasma colonisation is suspected of playing a role in preterm birth and preterm rupture of the membranes. Antibiotics are used to treat infections and have been used to treat pregnant women with preterm prelabour rupture of the membranes, resulting in some short-term improvements. However, the benefit of using antibiotics in early pregnancy to treat heavy vaginal colonisation is unclear.

Objectives

To assess whether antibiotic treatment of pregnant women with heavy vaginal ureaplasma colonisation reduces the incidence of preterm birth and other adverse pregnancy outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 May 2011).

Selection criteria

Randomised controlled trials comparing any antibiotic regimen with placebo or no treatment in pregnant women with ureaplasma detected in the vagina.

Data collection and analysis

Three review authors independently assessed eligibility and trial quality and extracted data.

Main results

We included one trial, involving 1071 women. Of these, 644 women between 22 weeks and 32 weeks' gestation were randomly assigned to one of three groups of antibiotic treatment (n = 174 erythromycin estolate, n = 224 erythromycin stearate, and n = 246 clindamycin hydrochloride) or a placebo (n = 427). Preterm birth data was not reported in this trial. Incidence of low birthweight less than 2500 grams was only evaluated for erythromycin (combined, n = 398) compared to placebo (n = 427) and there was no statistically significant difference between the two groups (risk ratio (RR) 0.70, 95% confidence interval (CI) 0.46 to 1.07). There were no statistically significant differences in side effects sufficient to stop treatment between either group (RR 1.25, 95% CI 0.85 to 1.85).

Authors' conclusions

There is insufficient evidence to assess whether pregnant women who have vaginal colonisation with ureaplasma should be treated with antibiotics to prevent preterm birth.

Preterm birth is a significant perinatal problem. Upper genital tract infections, including ureaplasmas, are suspected of playing a role in preterm birth and preterm rupture of the membranes. Antibiotics are used to treat women with preterm prelabour rupture of the membranes; this may result in prolongation of pregnancy and lowers the risks of maternal and neonatal infection. However, antibiotics may be beneficial earlier in pregnancy to eradicate potentially causative agents.

PLAIN LANGUAGE SUMMARY

Antibiotics for ureaplasma in the vagina in pregnancy

Ureaplasmas are normal flora in the vagina of many women. In some women high levels of ureaplasma in the vagina, which probably reflect the presence of infection in the uterus, may have a role in pregnancy complications, or may contribute to babies being born before full term (preterm birth), or both. These babies can have serious health problems. Some antibiotics can be safely used during pregnancy and are also active against ureaplasma. The authors identified only one trial (involving 1071 women) that was eligible for inclusion in this review. Therefore, there is insufficient data to assess whether giving antibiotics to women with ureaplasma in the vagina reduces the risk of preterm birth.

BACKGROUND

Preterm birth (less than 38 weeks' gestation) is a leading cause of mortality and morbidity (Gravatt 2010; Kramer 2000; Lawn 2010; Roberts 2000; Wood 2000). Globally, preterm birth occurs for approximately 13 million babies annually (Lawn 2010). Rates vary by many factors, including country of birth (Hall 1997), sociodemographic variables, race and ethnic groups. The causes of most spontaneous preterm birth are unknown and are most likely a complex relationship of causality (Lawn 2010). Known causal pathways tend to vary by gestation. Between the 22nd and 32nd week, inflammation caused by infection occurs commonly (Gravatt 2010). There is some evidence suggesting that genital colonisation, infections, or both, including with ureaplasmas, contribute to preterm labour and preterm rupture of membranes (Gilbert 1995; Goldenberg 2000).

Genital colonisation with ureaplasmas is common, and are normal flora carried by up to 80% of healthy women (McDonald 1997). They are usually harmless, presumably because the organisms stimulate a mucosal antibody response which controls their numbers and prevents local tissue invasion. In a small proportion of colonised women, ureaplasmas are found in the vaginal fluid in relatively high concentrations, presumably because they are poorly controlled by the host immune response. This may lead to ascending infection and subacute or chronic endometritis and contribute to infertility; and during pregnancy to complications such as spontaneous abortion or chorioamnionitis; and preterm birth may occur (Gilbert 1995). Whatever the mechanism, there is an association between preterm birth and ureaplasma colonisation or infection of the amniotic fluid, membranes, placenta and the infant (Gilbert 1995).

Ureaplasmas are the commonest isolates, often in pure culture, from the amniotic fluid and placentas of women who deliver prematurely and their presence is strongly associated with histological evidence of chorioamnionitis (Cassell 1993a; Hillier 1988). They are more commonly isolated from the respiratory tract of extremely preterm than from term infants, and their presence often is associated with congenital pneumonia and chronic neonatal lung disease (Cassell 1988; Hannaford 1999). Despite these associations, prospective studies have not shown a consistent association between lower vaginal colonisation and preterm birth (Cassell 1993b; McDonald 1992). Moreover, treatment during pregnancy has not consistently reduced the incidence of preterm birth (Eschenbach 1991; McGregor 1990). A 1995 review of two trials concluded that "there is no evidence currently to support the routine treatment at any stage of pregnancy of women found to be positive for *Ureaplasma urealyticum* to prevent prematurity" (Smaill 1995). The most likely explanation for the apparently contradictory findings is that the causes of preterm birth are multifactorial. There is evidence that other types of infection, including bacterial vaginosis, chlamydia and group B streptococcal infection, may predispose to preterm birth (Goldenberg 2000; McGregor 1990) and only a subset of women colonised with ureaplasmas is at risk of complications. Vaginal colonisation per se is a poor predictor of risk, but a cohort study showed that high-density vaginal ureaplasma colonisation (more than 1000 colony forming units/ml) was a risk factor for chorioamnionitis and preterm birth (Abele-Horn 2000).

Macrolide antibiotics, such as erythromycin, are one of the few agents active against ureaplasmas and can be safely used in pregnancy. Tetracyclines and fluoroquinolones are active against ureaplasmas but not used in pregnancy. For women with spontaneous preterm labour and intact membranes, treatment with antibiotics confers no clear benefit (Kenyon 2001; King 2002). However, for women with preterm prelabour rupture of the membranes treatment with antibiotics results in prolongation of pregnancy and lower risks of neonatal infection although the longer term health benefits are unclear (Kenyon 2010).

It may be possible to prevent the inflammatory cascade which is believed to lead to spontaneous preterm labour, preterm prelabour rupture of the membranes and preterm birth; however, we first need to identify women with abnormal genital colonisation who are at increased risk of infection and identify an appropriate treatment schedule suitable for use in early in pregnancy to eradicate their infection. The effectiveness of such treatment is likely to be affected by the type of antibiotic, the timing in pregnancy, dosage, duration of treatment and the route of administration. The purpose of this review is to assess whether antibiotic treatment of pregnant women with ureaplasma in the vagina reduces the incidence of preterm birth and other adverse pregnancy outcomes.

This review is separate to the 'Antibiotics for treating bacterial vaginosis in pregnancy ' Cochrane Review - please *see* McDonald 2007.

OBJECTIVES

Primary

To assess the effectiveness of antibiotics in reducing preterm birth among pregnant women with ureaplasma in the vagina.

Secondary

To assess the effectiveness of antibiotics in reducing other adverse pregnancy outcomes among pregnant women with ureaplasma in the vagina.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials that compared any antibiotic regimen with placebo or no treatment in pregnant women with ureaplasma detected in the vagina were eligible for inclusion. We excluded studies where the enrolment criteria was not ureaplasma in the vagina, or where women were included due to threatened preterm labour or premature rupture of the membranes, which were the outcomes of interest. *See* also Characteristics of excluded studies table.

Types of participants

Women of any age, less than 37 weeks' gestation, with detection of ureaplasma in the vagina regardless of method of detection (because of symptoms or as a part of a screening program). We excluded studies of women in preterm labour.

Types of interventions

Any antibiotic (any dosage regimen, any route of administration, commenced before 37 weeks' gestation) compared with either placebo or no treatment.

Types of outcome measures

Primary outcomes

Incidence of any preterm birth less than 37 weeks' gestation.

Secondary outcomes

1. Incidence of spontaneous preterm labour 32 to 36 weeks' gestation;
2. incidence of spontaneous preterm labour less than 32 weeks' gestation;
3. incidence of preterm prelabour rupture of the membranes (PPROM) 32 to 36 weeks' gestation;
4. incidence of PPROM less than 32 weeks' gestation;
5. incidence of low birthweight (however defined);
6. incidence of perinatal death (fetal and neonatal deaths);
7. severe neonatal morbidity (moderate to severe respiratory distress syndrome [defined as any ventilatory support] intraventricular haemorrhage, necrotising enterocolitis, chronic lung disease);
8. incidence of maternal intrapartum fever more than 38° Celsius;
9. incidence of maternal intrapartum antibiotic administration;
10. incidence of maternal postpartum (less than or equal to seven days) fever more than 38° Celsius;
11. incidence of maternal postpartum (less than or equal to seven days) antibiotic administration;
12. maternal side-effects sufficient to stop or change treatment;
13. maternal side-effects not sufficient to stop or change treatment;
14. failure to eradicate ureaplasma from the vagina (failure to achieve 'microbiological cure').

We planned the following a priori subgroup analyses:

- by gestational age at randomisation: less than 32 weeks, 32 to 37 weeks;
- by time of commencement of treatment;
- oral administration versus intravenous administration;
- presence of co-infection versus no co-infection;
- by class of antibiotic.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (31 May 2011).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

For the methods used when assessing the trials identified in the previous version of this review, *see* Appendix 1.

For this update, three review authors independently assessed for inclusion all the potential studies we identified as a result of the updated search (Eschenbach 1991; McCormack 1977; Ye 2001). There were no disagreements. We excluded all the new trials from the review - *see* Characteristics of excluded studies for the reasons for exclusion.

If new trials are included in future updates, we will use the methods described in Appendix 2.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We documented details regarding randomisation method, completeness of follow-up and blinding of outcome measurement for the one included trial.

Measures of treatment effect

We performed statistical analyses using the Review Manager software (RevMan 2011). We analysed dichotomous data using risk ratio (fixed-effect model) with 95% confidence intervals.

Unit of analysis issues

There were no included trials with non standard designs such as cross-over trials or cluster randomised trials.

Dealing with missing data

We made an a priori decision to exclude data from outcomes with more than 20% of participants missing. Analyses were by intention to treat. For included studies, we noted levels of attrition.

Assessment of heterogeneity

Assessment of heterogeneity not applicable as there is only one included study.

Assessment of reporting biases

Reporting of bias using funnel plots was not applicable due to only one included study.

Data synthesis

We did not undertake a meta-analysis. We have provided risk ratios from the one included trial.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were not possible due to the lack of studies; however, we planned the following a priori subgroup analyses:

- by gestational age at randomisation: less than 32 weeks, 32 to 37 weeks;
- by time of commencement of treatment;
- oral administration versus intravenous administration;
- presence of co-infection versus no co-infection;
- by class of antibiotic.

RESULTS

Description of studies

We identified one eligible study for this review (McCormack 1987), which between 1971 and 1980, enrolled pregnant women who after vaginal culture were positive for *Mycoplasma hominis* and/or *Ureaplasma urealyticum*, and whose gestations were between the 22nd and 32nd week. Participants were randomly allocated to receive either erythromycin estolate or stearate, clindamycin hydrochloride or placebo. Treatment was changed approximately half way through the study (in 1975). Erythromycin estolate was shown to be related to slight reversible elevations of serum aspartate aminotransferase (transaminase) levels, and clindamycin hydrochloride to excessive diarrhoea and other symptoms. These two treatments were stopped and patients were, from then on, randomised to receive 250 mg erythromycin stearate or placebo. Therefore, final numbers were unevenly distributed: 174 women received erythromycin estolate, and 246 clindamycin hydrochloride before they were discontinued. After the change in treatment, 224 women received erythromycin stearate and 427 placebo.

Treatment non-adherence was assessed and defined as having taken less than 50% of the capsules or having missed capsules for four (or more) consecutive days. Women who did not adhere to treatment schedule were excluded. There were no significant differences in adherence between either of the treatment arms. Laboratory evidence of toxicity was sought and measured at the two visits (two and four weeks after treatment commenced), and was also an exclusion criterion. Women who had symptoms which may have been due to the study treatment were also excluded from some analyses. The primary outcome measure and sample size calculations were not reported. The only outcome reported for all women randomised was number of women who discontinued treatment and the reason for discontinuation (including side effects). Data on mean birthweight and the rate of low birthweight (less than or equal to 2500 grams) were reported for all women who were randomised to erythromycin (either estolate or stearate) and placebo. *See* also Characteristics of included studies table. All other outcomes had loss to follow-up for more than 20% of participants and thus we have excluded these data from the review.

Risk of bias in included studies

We extracted methodological details of the one eligible and included study from the published paper only (McCormack 1987). Randomisation was reported but the method of concealment was not stated. A placebo was used, and it is reported that all capsules were identical and had been dispensed in bottles identified only by a code number, thus suggesting that participants were blinded to their treatment.

Intention-to-treat analysis was not conducted (except for two outcomes) as women who did not satisfactorily comply with treatment were excluded. Participants were excluded after enrolment and randomisation if they had not taken any of the treatment, had taken less than half of their treatment, had missed treatment on four (or more) consecutive days, or had symptoms that were related to the study drug. Sufficient follow-up was only available for two of the secondary outcomes; 'side-effects sufficient to stop treatment' data available for all women, and 'low birthweight' was available for women randomised to erythromycin (either preparation) or placebo.

Effects of interventions

In the one eligible trial, a total of 1105 women were enrolled between the 22nd and 32nd weeks of gestation. Of these 34 were identified as being not evaluable post-randomisation: 12 birthed twins, six were not pregnant, and 16 were lost to follow-up. Thus the remaining 1071 women were compared. Of these, 644 received antibiotic treatment (174 erythromycin estolate, 224 erythromycin stearate and 246 clindamycin hydrochloride) and 427 received a placebo. The uneven distribution of the groups can be explained through the change in treatment approximately halfway through the study; erythromycin estolate and clindamycin hydrochloride were prematurely stopped and erythromycin stearate replaced these. Over 50% of women were excluded from the analysis due to poor adherence; however, for two secondary outcomes, data for all women were collected and are included in this review.

Primary outcomes

There were no data to assess the effectiveness of antibiotics in reducing the incidence of preterm birth among women with ureaplasma in the vagina.

Secondary outcomes

Data were only available for two secondary outcomes.

'Low birthweight less than 2500 grams': there was no statistically significant difference between the group randomised to erythromycin (either preparation) or placebo group (relative risk (RR) 0.70, 95% confidence interval (CI) 0.46 to 1.07). Data from 825 women contributed to this outcome: erythromycin combined groups (n = 174 + 224) and the placebo group (n = 427).

'Maternal side-effects sufficient to stop or change treatment': there was also no statistically significant difference between the antibiotic groups (combined) and the placebo group (RR 1.25, 95% CI 0.85 to 1.85), although women who were taking any antibiotic were more likely to report symptoms that were sufficient to stop (erythromycin estolate 10.9%, erythromycin stearate 8.9% and clindamycin hydrochloride 11.0%). Data from 1071 women contributed to this outcome.

DISCUSSION

The data for this review are insufficient to assess the effectiveness of antibiotics in treating ureaplasma colonisation in the vagina to reduce the incidence of adverse pregnancy outcomes.

Although other studies appeared to meet the inclusion criteria for this review, ureaplasma was not an essential entry criterion (e.g. McGregor 1988; Paul 1998). Some studies have reported a post hoc subgroup analysis of ureaplasma (e.g. Ogasawara 1997). We have not included these studies, as the publication of post hoc subgroup analyses usually implies that a positive result was found and therefore introduces bias. Another trial met the inclusion criteria but did report the number of women randomised or excluded and subsequently only included data on subgroup analyses (Eschenbach 1991).

There have been no new trials investigating this intervention in this population since the late 1990s and although the role of infection in preterm birth continues to be an important question, the actual mechanism of the infection cascade needs to be better understood before intervention questions such as type of treatment, dosage and gestation can be answered. Equivocal results of antibiotic treatment suggest that we do not yet understand the mechanism.

AUTHORS' CONCLUSIONS

Implications for practice

There are limited implications for practice, given the insufficient evidence to support or refute the use of antibiotic treatment for ureaplasma in the vagina with the intent of preventing preterm birth.

Implications for research

The role of vaginal colonisation of *Ureaplasma urealyticum* remains unknown and intervention trials are unlikely while the precise causal pathway remains unclear. To test the efficacy of antibiotic treatment in this group of women, a large well-designed trial is needed. However given the high prevalence of *Ureaplasma urealyticum* in the population, it is important to identify those women at risk of preterm birth before the commencement of a treatment trial.

ACKNOWLEDGEMENTS

We thank Caroline Crowther and David Henderson-Smart for helpful comments during the protocol stage of this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

McCormack 1987

Methods	Type of study: single centre randomised trial. Method of treatment allocation: 'randomized'. Placebo: yes. Sample size calculation: not stated. Intention-to-treat analysis: only for 2 outcomes. Losses to follow-up: 34 were not evaluable, 620 did not comply with the treatment regimen and were excluded from some outcomes. Funding: grant from the National Institute of Child Health and Human Development, USA.
Participants	Location/time: Boston, USA. 1971-1980. Eligibility criteria: pregnant women whose vaginal culture contained *M hominis* and/or *U urealyticum*, their urine culture contained fewer than 10,000 bacteria/mL, and no renal, hepatic or hematological abnormalities. Exclusion criteria: history of adverse reaction to erythromycin, history of liver disease, or presence of other condition that would require antimicrobial treatment. Enrolled: 1105, 34 not evaluated, 1071 compared for some outcomes.
Interventions	Identical capsules of erythromycin estolate (250 mg) (n = 174), or clindamycin hydrochloride (150 mg) (n = 246), or placebo. Due to adverse effects, in 1975 erythromycin estolate and clindamycin hydrochloride were no longer used and were replaced by erythromycin stearate. Thereafter, participants were randomised to receive either erythromycin stearate (n = 224) or placebo (n = 427). Dose: 1 x 4 daily for 6 weeks (capsules).
Outcomes	Primary: not stated. Secondary: maternal: side effects sufficient to stop at 3 or 6 weeks. Mycoplasmal colonisation, 3 and 6 weeks after treatment. antibodies to *U urealyticum* and *M hominis*. Characteristics of labour and delivery. Infant: birthweight < 2500 g. Congenital malformations.
Notes	At 3 and 6 weeks women's adherence with treatment schedule was reviewed - if women had taken more than half of capsules without a break of 4 consecutive days, they were eligible for analysis. At 6 weeks only 451/1071 (42%) were considered compliant. Erythromycin estolate and clindamycin hydrochloride were discontinued during the study period due to excess of side effects. Slight reversible elevated amino-transferase > 10% of participants (due to EE), and excess of diarrhoea and other symptoms (due to CH) were reported. These therapies were replaced by erythromycin stearate, and women were randomly assigned to this or a placebo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States 'randomized' but method is unclear.
Allocation concealment (selection bias)	Unclear risk	Not reported.

McCormack 1987 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	A placebo was used, and it is reported that all capsules were identical and had been dispensed in bottles identified only by a code number.

CH: clindamycin hydrochloride
EE: erythromycin estolate

Characteristics of excluded studies *[ordered by study ID]*

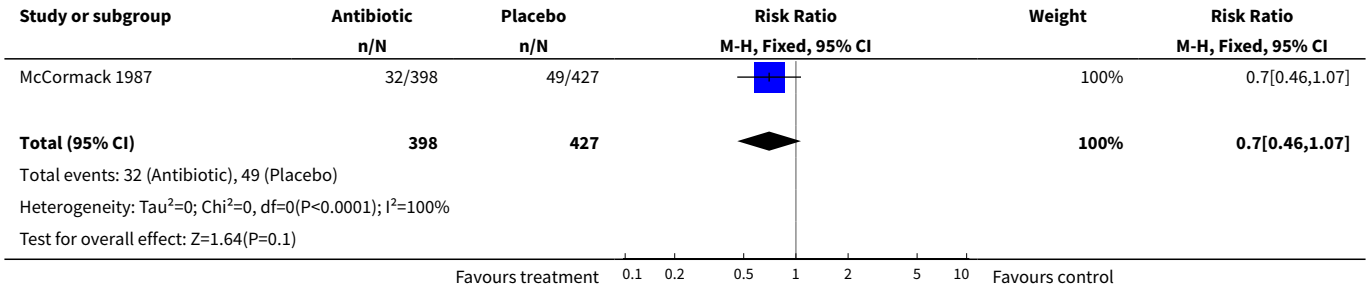
Study	Reason for exclusion
Eschenbach 1991	The number of women randomised and the number excluded were not reported. We have been unable to contact the author to clarify the numbers for this study. The data published are for the subgroup of women who have both ureaplasma and group B streptococcus in the vagina.
Hauth 1995	Women were enrolled on the detection of bacterial vaginosis.
Hauth 2001	Women were enrolled on the basis of threatened preterm labour, and not on detection of *Ureaplasma urealyticum* in the vagina.
Kass 1986	Women were enrolled on the detection of other cervicovaginal micro-organisms which did not necessarily include *Ureaplasma urealyticum*.
McCormack 1977	This trial only reports on 1 outcome, level of serum glutamic oxalacetic transaminase (SGOT). This is not an outcome of interest for this review.
McGregor 1988	Women were enrolled on the detection of various cervicovaginal micro-organisms which did not necessarily include *Ureaplasma urealyticum*.
Ogasawara 1997	Women were enrolled on the basis of threatened preterm labour, or with preterm premature rupture of the membranes and not on detection of *Ureaplasma urealyticum* in the vagina.
Ogasawara 1999	Women were enrolled on the basis of threatened preterm labour, or with preterm premature rupture of the membranes and not on detection of *Ureaplasma urealyticum* in the vagina.
Paul 1998	Women were enrolled on the detection of cervicovaginal micro-organisms which did not necessarily include *Ureaplasma urealyticum*.
Winkler 1988	Women were enrolled on the basis of threatened preterm labour, and not on detection of *Ureaplasma urealyticum* in the vagina.
Ye 2001	Chinese publication with translation to English. It is unclear from this translation what treatment, if any, was allocated to the control group. In addition it is not possible to adequately determine the methodology used in this trial.

DATA AND ANALYSES

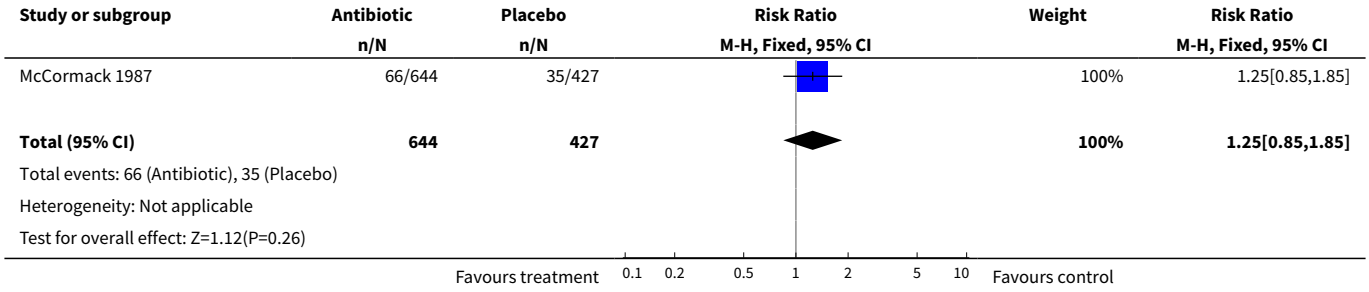
Comparison 1. Antibiotic versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Low birthweight < 2500 g	1	825	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.46, 1.07]
2 Maternal side effects sufficient to stop or change treatment	1	1071	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.85, 1.85]

Analysis 1.1. Comparison 1 Antibiotic versus placebo, Outcome 1 Low birthweight < 2500 g.



Analysis 1.2. Comparison 1 Antibiotic versus placebo, Outcome 2 Maternal side effects sufficient to stop or change treatment.



APPENDICES

Appendix 1. Methods used to assess trials included in previous versions of this review

Three reviewers independently assessed the trials for inclusion in the review. We assessed the methodological quality of each trial to be included according to criteria in the Cochrane Reviewers' Handbook (Clarke 2003), with a grade allocated to each trial on the basis of allocation concealment: A (adequate), B (unclear), C (clearly inadequate). We documented details regarding randomisation method, completeness of follow up and blinding of outcome measurement for all trials. We excluded quasi-randomised designs, such as alternate allocation and use of record numbers. We resolved any differences of opinion regarding trials for inclusion by discussion. We made an a priori decision to exclude data from outcomes that were unavailable for more than 20% of participants.

Three reviewers independently extracted the data using prepared data extraction forms. Any discrepancies were resolved by discussion. We performed statistical analyses using the Review Manager software (RevMan 2000). We analysed categorical data using relative risk, risk difference and number needed to treat.

Appendix 2. Methods to be used in future updates

Data extraction and management

We will design a form to extract data. For eligible studies, at least two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. We will enter data into Review Manager software (RevMan 2011) and check for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by involving a *[third]* assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator),
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number) or,
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel;

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by 1 to 5 above)

We will describe for each included study any important concerns we have about other possible sources of bias.

We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the Handbook (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* 'Sensitivity analysis'.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised trials. We will adjust their sample sizes or standard errors using the methods described in the Handbook using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity or subgroup analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of

whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if I^2 is greater than 30% and either T^2 is greater than zero, or there is a low P-value (< 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by Egger 1997, and for dichotomous outcomes we will use the test proposed by Harbord 2006. If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2011). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials.

If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

WHAT'S NEW

Date	Event	Description
31 May 2011	New search has been performed	Search updated. Three trial reports have been assessed, resulting in two new excluded studies (McCormack 1977; Ye 2001) and one additional report added to a previously excluded study (Eschenbach 1991).
31 May 2011	New citation required but conclusions have not changed	New author helped to update the review.

HISTORY

Protocol first published: Issue 3, 2002
Review first published: Issue 1, 2004

Date	Event	Description
1 October 2009	Amended	Search updated. Three reports added to Studies awaiting classification (McCormack 1977a; Nugent 1988a; Ye 2001a).
25 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Camille Raynes-Greenow gathered background information, appraised the quality of papers, entered the data into RevMan and is primary author for the review. The original review was conceived by Christine Roberts who also appraised the quality of the papers, and assisted with the original drafts. Jane Bell screened the retrieved papers against inclusion criteria, appraised the quality of the papers and provided

editorial assistance for the original review and the update. Gwendolyn Gilbert and Brian Peat provided content expertise (microbiological and obstetric respectively) and reviewed drafts of the review and the update (GG). Sharon Parker appraised the quality of the papers for the update, entered data into RevMan, contributed to writing and overall production of the update.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Centre for Perinatal Health Services Research, Australia.
- NHMRC Post-doctoral Public Health Fellowship, Not specified.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no differences between the protocol and the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Clindamycin [therapeutic use]; Erythromycin [analogs & derivatives] [therapeutic use]; Erythromycin Estolate [therapeutic use]; Pregnancy Complications, Infectious [*drug therapy] [microbiology]; Randomized Controlled Trials as Topic; Ureaplasma Infections [*drug therapy]; Vaginal Diseases [*drug therapy] [microbiology]

MeSH check words

Female; Humans; Pregnancy